Remarks

Claims 2-6 and 8-42 are pending. Claims 5 and 8-41 are withdrawn. Applicants respectfully request reconsideration and allowance of claims 2-4, 6, and 42 in view of the following remarks.

Rejection of Claims under 35 U.S.C. § 103(a)

Claims 2-4, 6 and 42 are rejected under 35 U.S.C. § 103(a) as obvious over WO 97/26328 in view of Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997), Rammensee *et al.* (MHC Ligands and Peptide Motives, LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281), WO 99/45954, US 7,063,854 and Sievers (Curr. Opin. Immunol. 12:30-35, 1/00). Applicants respectfully traverse the rejection.

Claims 2-4, 6 and 42 are also rejected under 35 U.S.C. § 103(a) as obvious over WO 97/26328 in view of Leukocyte Antigen Fact Book (2nd edition, pages 244-247, 1997), Rammensee *et al.* (MHC Ligands and Peptide Motives, LANDES Bioscience, Springer, NY, 1997, pages 217-227 and 236-281), US 6,602,510; US 7,063,854 and Sievers (Curr. Opin. Immunol. 12:30-35, 1/00). Applicants respectfully traverse the rejection.

None of the cited references, alone or in combination, disclose or suggest each element of the claims or provide motivation to modify the references as Applicants have done with any reasonable degree of success.

Legal Standard

The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquires may have relevancy. . .
>
> This in not to say, however, that there will not be difficulties in applying the nonobviousness test. What is obvious is not a question upon which there is likely to be uniformity of thought in every given factual context. The difficulties, however, are comparable to those encountered daily by the courts in such frames of reference as negligence and scienter, and should be amenable to a case-by-case development. We believe that strict observance of the requirements laid down here will result in that uniformity and definitiveness which Congress called for in the 1952 Act.

Thus, a determination of obviousness must include a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d

1438 (Fed. Cir. 1991). Mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. *In re Kahn*, 441 F.3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 USPQ2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 USPQ 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. See *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court Appeal for the Federal Circuit has consistently held that "'obvious to try' is not to be equated with obviousness under 35 USC 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 USPQ2d 1923, 1928 (Fed. Cir. 1990).

Analysis

Claims 2-4, and 6, and 42

Claim 2 is independent and defines a peptide of about 9 to 12 amino acid residues, wherein the peptide comprises an HLA-binding peptide of the human CD45 polypeptide comprising the amino acid sequence FLYDVIAST (SEQ ID NO:1) or a variant of SEQ

ID NO:1, wherein the variant contains an amino acid substitution at position 2, 9 or both. Claims 3-4, 6, and 42 depend from claim 2.

Claim 3 further requires that the peptide of claim 2 is capable of binding to HLA-A0201.

Claim 4 depends from claim 3 and requires that when bound to HLA-A0201 the peptide-bound HLA-A0201 is capable of eliciting the production of a cytotoxic T lymphocyte (CTL) which recognizes a cell which expresses a polypeptide comprising the HLA-binding peptide of human CD45 polypeptide.

Claim 6 depends from claim 2 and requires the peptide to have the sequence FLYDVIAST (SEQ ID NO:1).

Claim 42 depends from claim 2 and requires the peptide to have the sequence FLYDVIAST (SEQ ID NO:1).

The Examiner Failed to Establish a Prima Facie Case of Obviousness

The Examiner failed to establish a prima facie case of obviousness in the Office Action mailed on September 21, 2006, for at least the reasons that the cited references, alone or in combination, fail to disclose or suggest each element of the claims, fail to provide some suggestion or motivation to combine the references, and one of ordinary skill would not have a reasonable expectation of success to produce the claimed peptide based on these references.

WO 97/26328 Fails to Disclose or Suggest Each Element of the Claims.

Page 24, lines 5-6 of the specification of the above-referenced application cites WO 97/26328 as disclosing methods of treatment using allo-restricted cytotoxic T lymphocytes (CTLs). As noted by the Examiner on pages 2 and 7 of the Office Action

mailed on September 21, 2006, WO 97/26328 teaches generating CTLs specific for peptides that are expressed in leukemic cells but not in cells outside the hematopoietic lineage (page 23, lines 12-14). WO 97/26328 lists numerous antigens that can be used to generate allo-restricted CTLs. Representative antigens include: (i) normal self antigens expressed at high levels in tumor cells; (ii) mutated self antigens expressed in tumor cells; or (iii) viral antigens expressed in tumors associated with viral infection.

Category (i) includes a) normal cellular proteins that are overexpressed; b) proteins that are expressed in a tissue-specific fashion in normal cells but also in tumors; and c) proteins that are embryonic antigens, silent in most adult tissues but aberrantly expressed in tumors. Representative tissue-specific differentiation antigens include GATA- 1, IKAROS, SCL, WT 1, GATA- 1 and IKAROS (page 23, lines 19-23). These proteins are DNA binding proteins expressed only in hematopoietic cells. *Id.*
WO 97/26328 does not disclose or suggest that membrane bound cytokine receptors such as CD45 can be successfully used to generate allo-restricted CTLs for treating leukemia. The teaching that intracellular DNA binding proteins can be used to generate allo-restricted CTLs, WO 97/26328 teaches away from using membrane bound cytokine receptors such as CD45. Indeed, the Examiner concedes that WO 97/26328 fails to disclose or suggest allo-restricted CTLs specific for fragments of CD45. Therefore, WO 97/26328 fails to disclose or suggest each element of claimed peptide or variants thereof. Additionally, WO 97/26328 also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

The Leukocyte Antigen Fact Book Fails to Disclose or Suggest Each Element of the Claims.

The Leukocyte Antigen Fact Book discloses that CD45 is found in all cells of hematopoietic origin except erythrocytes. The reference also provides the amino acid sequence of CD45. The Leukocyte Antigen Fact Book fails to disclose or suggest each element of the claims because it does not teach or suggest peptides of CD45 that bind to HLA or variants thereof. Additionally, Leukocyte Antigen Fact Book also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

Rammensee *et al.* Fails to Disclose or Suggest Each Element of the Claims.

Rammensee *et al.* discloses that most MHC class 1 molecules use two primary anchor residues, one of which is the C-terminal amino acid and the other is the second residue from the N-terminus, although auxiliary anchors may be present. According to the Table on page 237, the primary anchor residues for HLA-A0201 are L or M at position 2, and V or L at position 9, together with a V at position 6 as an auxiliary anchor. Although the L at position 2 is present in the sequence of SEQ ID NO: 1, T at the C-terminal position is not one of the primary anchor residues for binding to HLA-A0201 taught by Rammensee *et al.*

The Table on page 237 also specifies a number of preferred residues for a peptide which binds to HLA-A0201 and these are E at position 4 and K at position 8 or K at position 4. None of these are found within the sequence of SEQ ID NO: 1.

The Table on page 237 further specifies a third level of preferences for the amino acid residues at various positions within a peptide that binds to HLA-A0201. However,

none of the combinations of amino acids discloses or suggest T as the C-terminal anchor position as required by the claims. Therefore, Rammensee *et al.* fails to disclose or suggest the claimed peptide or variants thereof. Rammensee *et al.* also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

WO 99/45954 Fails to Disclose or Suggest Each Element of the Claims.

Page 5 of WO 99/45954 describes the peptide motifs recognized by HLA-A2.1 alleles for peptides of both 9 and 10 residues in length. For a 9 residue peptide, the first conserved residue (anchor residue) is at the second position from the N-terminus and is selected from I, V A or T and the second conserved (anchor) residue is at the C-terminal position and is selected from V, L I, A and M (lines 7-10). The alternative motif given on page 5 (lines 10-14) is one in which the conserved residue at position 2 is L, M, I, V, A or T and the conserved C-terminal residue is A or M. Since the peptide of SEQ ID NO: 1 (FLYDVIAST) does not have any of the conserved anchor residues at the C-terminal position taught in WO 99/45954, this reference also cannot make the claimed peptide obvious. Indeed, it teaches away for the claimed subject matter because it teaches that the C-terminal anchor residue is V, L, I, A or M.

The HLA-A2.1 binding motif for peptides of 10 residues in length has a conserved amino acid at position 2 which is selected from L, M, I, V, A and T and a second conserved anchor residue at the C-terminus selected from V, I, L, A and M. The first and second conserved residues are separated by seven amino acid residues. Again, since the peptide of SEQ ID NO: 1 (FLYDVIAST) has T at the C-terminal position, and

this is not one of the anchor residues at that position taught by WO 99/45954, this document cannot render the claimed peptide obvious.

WO 99/45954 also teaches which amino acid substitutions can be made to the peptide while changing its function or activity to a greater or lesser extent. For example, exemplary conservative substitutions are listed on page 12, lines 15-16 and Table 2 on page 14. By contrast, according to page 15, lines 1-3, substantial changes in function, e.g. affinity for MHC molecules, can be made by using a substitution that is less conservative than those in Table 2.

In Table 2, the only conservative substitution involving T (Thr) is with S (Ser). Therefore, WO 99/45954 teaches that replacing the C-terminal anchor residue V, I, L, A or M with T would be a non-conservative change that is expected to lead to a "substantial change in function, e.g. affinity for MHC molecules". Accordingly, when attempting to identify a peptide from CD45 that binds to HLA-A2.1, WO 99/45954 teaches away from a peptide with T at the C-terminus. Thus, WO 99/45954 fails to disclose or suggest the claimed peptide or variants thereof. WO 99/45954 also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

U.S. Patent No. 6,602,510 Fails to Disclose or Suggest Each Element of the Claims.

U.S. Patent No. 6,602,510 (Fikes *et al.*) discloses the supermotif for peptides to bind to HLA-A2 as well as the motif for binding to HLA-A0201. Although Fikes *et al.* disclose various binding motifs for peptides, Fikes *et al.* fails to disclose or suggest CD45 peptides that bind to HLA or the claimed variants thereof. Fikes *et al.* also fails to

provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

U.S. Patent No. 7,063,854 Fails to Disclose or Suggest Each Element of the Claims.

U.S. Patent No. 7,063,854 (Gaiger *et al.*) is directed to Wilms Tumor 1 (WT1) peptides useful for treating cancer (Abstract). Gaiger *et al.* does not disclose or suggest a CD45 peptide according to SEQ ID NO:1 or variants thereof. CD45 is mentioned twice in Gaiger *et al.,* once at Column 28, line 38, and then at Column 28, lines 61-64. Column 28, line 38 discloses an undefined CD45 peptide used as a control for immunizing mice. Column 28, lines 61-64 disclose that CD45 can be used to stimulate T-cells. The Examiner cites the Abstract; column 28 at lines 53-64; column 29; column 30 at Table III; column 61; claims; column 18 at lines 27-67; column 19; column 20 at lines 1-61 as disclosing methods for predicting CD45 peptides that bind to HLA-A*0201. Applicants respectfully submit that the Examiner is misreading Gaiger *et al.*

For example, the Abstract does not mention CD45. Column 28, lines 53-64 as discussed above, shows that CD45 can be used to stimulate T-cells. It does not disclose the CD45 peptide according to SEQ ID NO:1.

Column 29 includes Example 4 which is entitled "Induction of CTL Responses in Mice Immunized with WT1 Peptides." Column 29 does not disclose CD45 peptides.

Column 30 at Table III discloses WT1 peptides and human HLA binding predictions. Column 30 does not disclose CD45 peptides.

Column 61 discloses WT1 peptides and binding predictions of these WT1 peptides. Peptides of CD45 are not listed in Column 61.

The claims of Gaiger *et al.* define compositions containing an immunogenic portion of WT1.

Column 18, lines 27-67 disclose pharmaceutical compositions and vaccines including WT1 polypeptides or an antigen presenting cell transfected with WT1 polynucleotide. Column 18, lines 27-67 does not disclose CD45 peptide according to SEQ ID NO:1.

Column 19 discloses that WT1 can be used in vaccines and pharmaceutical compositions. Column 20 continues with descriptions of pharmaceutical compositions and vaccines containing WT1 polypeptides. Columns 19 and 20 do not mention CD45.

Thus, contrary to the Examiner's assertion, Gaiger *et al.* does not disclose or suggest predicting HLA-A*0201 binding peptides from CD45. Gaiger *et al.* also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

Sievers Fails to Teach or Suggest Each Element of the Claims.

Sievers (2000) Curr. Opin. Immunol. 12:30-35 ("Sievers") discloses that CD45 can be used as a target to selectively deliver chemotherapeutic agents conjugated to antibodies that bind to CD45 to hematopoietic cells. Sievers does not disclose or suggest CD45 peptides according to SEQ ID NO:1, variants thereof, or that such peptides can be used to generated allo-restricted CTLs that can be used to treat leukemia. Sievers also fails to provide any motivation to modify the references as Applicants have done with any reasonable expectation of success.

The Combination of WO 97/26328 in view of Leukocyte Antigen Fact Book, Rammensee *et al.*, WO 99/45954, US 7,063,854 and Sievers Fails to Teach or Suggest Each Element of the Claims.

The combination of WO 97/26328 in view of Leukocyte Antigen Fact Book, Rammensee *et al.*, WO 99/45954, US 7,063,854 and Sievers does not disclose or suggest each element of the claims. Specifically, the combined references do not disclose or suggest a peptide according to SEQ ID NO:1 which binds to HLA or variants thereof. Rammensee *et al.* and WO 99/45954 are cited as disclosing motifs of peptides that bind to HLA*0201. As discussed above, Rammensee *et al.* and WO 99/45954 fail to teach or suggest the peptide according to SEQ ID NO:1. Indeed, Rammensee *et al.* teach away from the peptide according to SEQ ID NO:1 because Rammensee *et al.* discloses peptides in which T is not the C-terminus anchor. The combination of the references with WO 99/45954 does not disclose or suggest the claim peptides because WO 99/45954 discloses peptides in which the C-terminal anchor residue is V, L, I, A or M. Thus, Rammensee *et al.* and WO 99/45954 fail to disclose or suggest a peptide that binds to HLA*0201 having a T at the C-terminus. The remaining references do not cure this deficiency. Thus, the combination of WO 97/26328 in view of Leukocyte Antigen Fact Book, Rammensee *et al.*, WO 99/45954, US 7,063,854 and Sievers cannot render claims 2-6 and 42 obvious.

One of Ordinary Skill In the Art Would Not Be Motivated to combine WO 97/26328, Leukocyte Antigen Fact Book, Rammensee *et al.*, WO 99/45954, US 7,063,854 and Sievers.

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. See *In re Geiger*, 815 F.2d 686, 2 USPQ2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984). *In re Laskowski*, 871 F.2d 115

(Fed. Cir. 1989). The Examiner argues that the motivation to combine the references is found in WO 97/26328 and the Leukocyte Antigen Fact Book. Applicants respectfully disagree.

WO 97/26328 lists numerous antigens that can be used to generate allo-restricted CTLs. Representative antigens include: (i) normal self antigens expressed at high levels in tumor cells; (ii) mutated self antigens expressed in tumor cells; or (iii) viral antigens expressed in tumors associated with viral infection. Category (i) includes a) normal cellular proteins that are overexpressed; b) proteins that are expressed in a tissue-specific fashion in normal cells but also in tumors; and c) proteins that are embryonic antigens, silent in most adult tissues but aberrantly expressed in tumors. There is no suggestion or even mention of using leukocyte common antigen to produce allo-restricted CTLs. Thus, WO 97/26328 is merely an invitation to experiment.

The Leukocyte Antigen Fact Book discloses that CD45 is expressed in cells of hematopoietic lineage except erythrocytes. There is no suggestion in the Leukocyte Antigen Fact Book that CD45 can be used to create a peptide according to SEQ ID NO:1 that binds to HLA or variants thereof. One of ordinary skill in the art would not be motivated to combine the Leukocyte Antigen Fact Book with WO 97/26328 because there is no indication in either reference that CD45 can be used to produce a peptide according to SEQ ID NO:1 that successfully binds to HLA*0201.

The Examiner then cites Sievers as teaching that CD45 is a target antigen for leukemic cells. Applicants submit that the Examiner is misapplying Seivers. Sievers discloses using conjugated antibodies that bind to CD45 to deliver chemotherapeutic agents to cells. Sievers does not disclose or suggest peptides of CD45 that bind to

HLA*0201. One of ordinary skill in the art would not be motivated to combine Sievers with the Leukocyte Antigen Fact Book, Rammensee *et al.* and WO 97/26328 because there is no teaching or suggestion in any of the references either expressly or inherently that a CD45 peptide according to SEQ ID NO:1 or variants thereof that can successfully bind to HLA*0201 to produce allo-restricted CTLs. Indeed, Sievers teaches intact CD45 is used as a target, not peptides of CD45. The method of using CD45 as a target for delivering chemotherapeutic agents conjugated to antibodies is vastly different than making modified peptides of CD45 that successfully bind to HLA*0201 to produce allo-restricted CTLs. An antibody-based treatment is not the same as a cell-based treatment. One of ordinary skill in the art would not be motivated to combine Sievers which discloses an antibody-based leukemia treatment with WO 97/26328 which discloses a cell-based leukemia treatment. Moreover, even if one were to combine the references, one or ordinary skill in the art would not have a reasonable expectation of success in view of the teaching in Fikes *et al.* which states that not all possible epitopes generate a CTL and HTL response (col. 20, lines 32-33).

U.S. Patent No. 7,063,854 to Gaiger *et al.* is cited as teaching the prediction of CD45 peptides binding to HLA*0201. As discussed above, the Examiner is misapplying Gaiger *et al.* Gaiger *et al.* merely used CD45 peptides as a control and discloses that CD45 antigen stimulates T-cells. The peptides disclosed in Gaiger *et al.* are WT1 peptides. Because Gaiger *et al.* does not disclose or suggest CD45 peptides that successfully bind to HLA*0201, one of ordinary skill in the art would not be motivated to combine the cited references as urged by the Examiner.

None of the cited references either alone or in combination disclose or suggest the claimed peptide or variants thereof. Sievers and Gaiger *et al.* do not teach what the Examiner alleges they teach. Fikes *et al.* teach that not all epitopes will elicit a CTL response. The remaining references do not cure the deficiencies in Sievers and Gaiger *et al.*

Finally, Applicants submit that the examiner is improperly engaging in hindsight analysis. The Examiner has cobbled together six different references to support the rejection. As discussed above, two of the references do not teach or suggest what the Examiner alleges. Accordingly, Applicants respectfully request the rejection be withdrawn.

One of Ordinary Skill in The Art Would Not be Motivated to Combine WO 97/26328 with Leukocyte Antigen Fact Book, Rammensee *et al.*, WO 99/45954, US 6,602,510, US 7,063,854 and Sievers.

Many of the cited references in the second rejection are the same as in the first rejection. The analysis of the references in common with the previous rejection is presented above and incorporated by reference. This rejection differs from the previous rejection in that the Examiner includes Fikes *et al.* in the rejection.

The Examiner cites Fikes *et al.* as disclosing peptides that bind to HLA-A2 supermotif in which L, I, V, M, A, T, or Q is at position 2 or the peptide and I, V, M, A, T, or L is at the carboxy-terminus. Fikes *et al.* disclose producing peptides from tumor-associated antigens such as CEA, p53, MAGE 2/3, and HER2/neu. Fikes *et al.* does not disclose or suggest using CD45 to produce peptides that bind to HLA*0201. The fact that a peptide could be made using the anchor residues taught by Fikes *et al.* does not render every peptide having the anchor residues taught by Fikes *et al.* obvious. The

Court of Appeals for the Federal Circuit has consistently held that "'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103." *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725, 16 USPQ2d 1923, 1928 (Fed. Cir. 1990).

The combination of references fails to provide a suggestion or motivation to combine the references and obtain a HLA-binding peptide according to SEQ ID NO:1 or a variant thereof. The Examiner alleges that it would have been obvious to use the method of epitope prediction taught by Fikes *et al.* to scan the sequence of the human CD45 leukemia tumor/differentiation antigen taught by Sievers to be a target for treatment of leukemia having the sequence disclosed in the Leukocyte Antigen Fact Book.

As discussed above, Sievers does not disclose or suggest HLA-binding peptides of CD45 or that such peptides can be used to treat leukemia by generating allo-restrict CTLs. Sievers discloses that CD45 can be used as a target to deliver chemotherapeutic agents conjugated to antibodies specific for CD45 to CD45 positive cells. Using antibodies to deliver chemotherapeutic agents to kill CD45 bearing cells is not the same as using allo-restricted CTLs that recognize HLA-binding CD45 peptides to kill CD45 bearing cells. Thus, one of ordinary skill in the art would not be motivated by the teachings of Sievers to combine or modify the remaining references.

Moreover, Fikes *et al.* clearly discloses that all possible epitopes that can be made do not cause a CTL or HTL response (col. 20, lines 32-33). Thus, Fikes et al. is merely an invitation to experiment with no reasonable expectation of success. Accordingly, one of ordinary skill in the art would not be motivated to combine the references.

Applicants respectfully submit that the claimed peptides and variants thereof are not obvious and it would not be obvious for one of ordinary skill in the art to try to produce the claimed peptide or variants thereof. The Examiner appears to be arguing that one of ordinary skill in the art would have synthesized peptides corresponding to all of the predicted sequences and tested each of them for ability to bind to HLA-A0201 and for their ability to generate CTLs. This is absolutely not the case because of the high level and cost of the work involved. The identification of FLYDVIAST by the inventors was a two-year research project at the approximate cost of $275,000. For the person of ordinary skill in the art to have synthesized each of the many peptides predicted by one of the methods of epitope prediction and assessed each and every one of these predicted peptides for their ability to bind to HLA-A0201 and to stimulate CTL would have been prohibitively expensive and require undue experimentation. The cited references do not provide sufficient guidance or motivation to enable one of ordinary skill in the art to arrive at the claimed peptide. Therefore, the combination of the cited references fails to render claims 2-6 and 42 obvious.

Variants of SEQ ID NO:1

Claim 2 also recites a HLA binding peptide variant of SEQ ID NO:1, wherein the variant contains an amino acid substitution at position 2, 9 or both. None of the cited references alone or in combination disclose or suggest such a variant of SEQ ID NO:1. Applicants respectfully submit that the claimed variants are free of the prior art of record.

Allowance of claims 2-6 and 8-42 is respectfully solicited.

Respectfully submitted,

/Charles Vorndran/
Charles Vorndran
Reg. No. 45,315

Date: March 21, 2007